ON THE ESCAPE OF THE HEART FROM VAGUS INHIBITION.

A Thesis

PRESENTED TO THE BOARD OF UNIVERSITY STUDIES OF THE JOHNS HOPKINS UNIVERSITY FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

BY

THEODORE HOUGH.

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ON THE ESCAPE OF THE HEART FROM VAGUS INHIBITION.

By THEODORE HOUGH, Ph.D. (Four Figures in Text.)

(*From the Biological Laboratory, Johns Hopkins University of Baltimore, U. S. A.*)

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1. INTRODUCTORY. THE ESCAPE OF THE HEART FROM VAGUS INHIBITION IS NOT THE RESULT OF THE EXHAUSTION OF THE FIBRES OF THE VAGUS NERVE.

Why does stimulation of the vagus nerve fail to keep the heart of a mammal at stand-still? This question has been frequently asked and has received various answers. It was formerly supposed that the fibres of the vagus are in some respect different from other nerve fibres in that they are more easily exhausted by stimulation; this exhaustion has, moreover, been attributed either to the continued conduction of nervous impulses to the end organ or to a loss of irritability at the

point of stimulation. The work of Wedenski, Bowditch, and others has, however, rendered very improbable the possibility of rapid exhaustion of a medullated nerve fibre, and the following experiment shows that this is not the explanation of the phenomenon under discussion: five or more centimetres of the cervical vagus are prepared and the peripheral portion laid in a metal trough, which can be cooled by a stream of water flowing around it; having determined the efficiency of inhibition, the peripheral portion of the nerve is cooled to the neighbourhood of 0° C., by which it is rendered non-conductive; the nerve is then stimulated centrally of this point for five or ten minutes; on warming the cooled portion of the nerve (by replacing the stream of cold water with one of warm water) it is found that the heart is brought to rest and remains inhibited as long as during the previous stimulation.

Here the nerve was evidently stimulated a much longer time than is ever required in the dog for the appearance of escape; it could not have been injured appreciably at the point of stimulation, and the conduction of impulses from this point to the cooled portion (over an inch intervened between the electrodes and the trough) could not have produced any exhaustion. In other words, so long as the inhibitory fibres remain fine medullated fibres of the vagus nerve they can be tired out neither by stimulation nor by conduction.

2. The Efficiency of Inhibition varies inversely with the Vigour of the Heart.

It is frequently stated that the more vigorous the heart the easier it is to bring about inhibition, and this seems to have been believed ever since the inhibitory action of the vagus was known. One reads, for example, in one of the best text-books of physiology in the English language: "When the nerve and the heart are in good condition, it needs only a slight stimulus, a weak current to produce a marked effect, *and it may be mentioned that the more vigorous the heart, the more rapidly it is beating, the easier it is to bring about inhibition.*"

I am not aware of the experiments upon which this statement is based, nor do I forget that it is made with reference to an animal (frog) upon which I have not worked, and whose cardiac vagus is peculiar in containing accelerator fibres. I am sure, however, that in the cat and the dog the more vigorous the heart, as shown by the pulse and blood-pressure, the more difficult it is to cause inhibition.

The comparative efficiency of vagus inhibition in strong and weak hearts respectively may be measured in several ways: (1) by the extent of slowing produced; (2) by the length of time the heart, if stopped, is held at stand-still; (3) by the rapidity or extent or both of escape during prolonged stimulation.

Whatever method be used we may either compare two animals, one of which apparently has a weaker heart than the other, or we may compare during the course of the same experiment the same heart under different conditions. It is seldom possible to keep an animal for two or three hours after the operation in exactly the same condition as regards rate of beat and pressure; it generally happens, especially in the case of cats, that there is a gradual weakening of the heart; the pulse will fall from 180—200 per minute to 120—140, and this will be accompanied by a fall of blood-pressure. It is fair, I think, to suppose that such a heart is not so vigorous at the end of the experiment as it was at the beginning. On the other hand it sometimes happens that the heart becomes more vigorous as the experiment progresses; the morphia, for instance, given to a dog as an anæsthetic may be an overdose; so that at first (*i.e.* some two hours after the injection) the heart is beating feebly and slowly; gradually toward the end of the experiment (one to two hours later) as the morphia is excreted a gradual improvement is noticed in the pulse.

It should, perhaps, be said that I have not specially investigated the question which is under discussion in this section of my paper; at the same time I think it can be shown that the numerous experiments with different strengths of current and upon animals in different conditions of nutrition, although made with other objects in view, afford unquestionable evidence on this point.

First, then, as to the extent of slowing with the same strength of stimulation in vigorous and weakened hearts respectively. Perhaps the best evidence of this kind is afforded by experiments upon cats. In a strong, healthy cat with the normal blood-pressure (120—180 mm. of mercury) and pulse (27—32 beats per ten seconds) it is almost, if not quite impossible to stop the heart by stimulation of one or both vagi with any strength of current whatever. I had made some twenty experiments on cats before a single case of stand-still occurred; usually upon stimulation blood-pressure falls for one or two seconds, but before complete diastole has occurred the beats recommence and the escape of the heart is comparatively rapid. For a full account of the conduct of the cat's heart during prolonged stimulation see page 183.

This is what always happens, unless for some reason or other the heart has been weakened; when, however, as the result of too much ether, chloral, or paraldehyde, or from any other cause the pulse is slow and more or less feeble, stimulation of the vagi is much more effective; the slowing of the heart and the fall of blood-pressure are more pronounced, the rate remains at a lower level; and in some cases quite prolonged stand-still is produced. This result is so constant, there not being in all my work a single exception to it, that I have given it as the first reason for believing that the weaker the heart, the more feebly it is beating, the more effective is vagus stimulation.

Experiments 41 and 46 may be cited as cases in point.

In experiment 41, 2½ grammes of paraldehyde dissolved in 60 c.c. of water were injected into the stomach; this was not quite sufficient to produce unconsciousness, so that a little ether was added; both vagi were cut and one or the other stimulated. As frequently happens with the cat, moderately strong stimulation with its resulting systemic changes brought about a loss of irritability of the cord and medulla, so that the animal ceased breathing and artificial respiration had to be used; by this means the animal was kept alive for more than an hour; both the rate of beat and the blood-pressure, however, remained low, indicating an enfeebled condition of the heart. Stimulation of one vagus under these conditions with strong or moderately strong currents was quite effective, as the following figures show; the pulse and pressure are given for each ten seconds. These figures should be compared with the results obtained on cats whose hearts were beating with normal force and frequency.

No.	Time			Fractions in secs.	Rate	Pressure	Remarks
	hrs.	min.	secs.				
II	3	44	20		19	61	
			30	5	11	49	L at 10
				5		35	
			40		10	31	
	3	45	30		15	44	
			40		18	45	Off
III	3	50	20		18	62	
			30		7	30	R at 5
			40		15	46	
	3	51	30		22	68	
			40		22	69	Off

No.	Time hrs.	Time min.	Time secs.	Fractions in secs.	Rate	Pressure	Remarks
IV	3	56	10		19	89	
			20	5	8	63	R at 10
				5		50	
			30		9	43	
	3	57	40		15	58	
			50		18	62	Off
X	4	42	40		20	82	
			50		6	42	R at 6
	4	53			6	50	
	4	55	20		16	59	
			30		16	63	
			40		20	69	Off

The results of most experiments are given in this form ; the first column gives the number of the tracing in the experiment; the second, the time; the fourth, the pulse ; and the fifth, the pressure. The time is given in periods of ten seconds; if for any reason it is advisable to give the rate and pressure for shorter periods of time this is indicated by the third column, which gives the fractions (in seconds) of that ten seconds. Thus in the second tracing of the above experiment the figures indicate that between 3hrs. 44mins. 30secs. and 3hrs. 44mins. 40secs. the heart gave eleven beats; that during the first five seconds of this period the average blood-pressure was 49mm. of mercury, and during the second five seconds 35 mm. of mercury.

In subsequent protocols it is to be understood that the period of stimulation is indicated in the last column, and that the stimulation is continued until some change is indicated in the same column. Thus 3.45.20, L at 6 means that at 45mins. 20secs. past three o'clock the left nerve was stimulated with the secondary coil of the induction apparatus 6 cm. from the primary coil. R means that the right nerve is stimulated; B that both are simultaneously stimulated. Cessation of stimulation is indicated by "Off."

Tracings 5, 6, 7, 8, and 9 of the above experiment give similar results to those shown in the table. In all cases the amount of slowing is much greater than occurs ordinarily in vigorous animals.

In experiment 46 a small cat was kept under the influence of ether during the operation, which the animal did not stand well; so that, although after the operation no ether was administered, not even the lid reflex was present. Artificial respiration. The pulse gradually sank from 21 to 14 beats per ten seconds, while the pressure at all times (largely due to failure of the vaso-motor centre to maintain the tone of the small arteries) was very low. More unfavourable conditions could

not well be desired; and the following figures will show that vagus stimulation was able in all cases to stop the heart.

No.	Time hrs.	Time min.	Time secs.	Fractions in secs.	Rate	Pressure	Remarks
I	3	24	10		21		
			20		0		3.24.20 R at 8
			30		0		
			40		14		
	3	26			17+		
			10		18		3.26.10 Off
			20		19		
VII	4	23			14		
			10		0		4.23.10 R at 8
			20		0		
			30	3	0		
				7	2		
			40		*3+		
	4	28	20		8		
			30		9		4.28.30 Off
			40		12		

* 3+ means that between 3 and 3½ beats were given; 4− between 3½ and 4 beats; a beat being measured between any two corresponding points of the cardiogram.

Tracings 4, 5, and 6 gave similar results.

For convenience of reference I insert the results of a typical tracing taken from a vigorous cat.

Exp. 22. Ether; both vagi cut and stimulated.

No.	Time hrs.	Time min.	Time secs.	Fractions in secs.	Rate	Pressure	Remarks
III	3	25	20		28	154	
			30		9	80	3.25.30 B at 6½
			40		12	82	
			50		17	93	
	3	28	10		23	126	

In what has just been said the efficiency of vagus stimulation in strong animals has been compared with that in weak ones, and it is evident that it is possible to greatly slow or even stop the heart of a weak animal by the use of a stimulus which in a vigorous animal is unable to do more than cause a comparatively slight and transient slowing followed by a rapid and almost immediate escape.

We now pass to a comparison of tracings taken from the same animal under different physiological conditions but during the same experiment. It should be remembered at the outset that the unavoid-

able presence of secondary factors or of slight experimental errors may at any time obscure the effect of the condition of the heart; such secondary factors are variations in the contact of the nerve with the electrodes, or of the strength of current in the primary circuit, or of the condition of the nerve itself; consequently we are not justified in comparing tracings, differences of which in rate and pressure are comparatively slight (say 5—20 beats per minute); it is only when the difference is considerable that we can expect the effect of the condition of the heart always to be apparent in the graphic record. Such comparisons leave no room for doubt.

Let us consider those experiments where a heart at first strong and vigorous became either suddenly or gradually weaker while under observation. During experiment 24 the first tracing gave the following result:

No.	Time			Fractions in secs.	Rate	Pressure	Remarks
	hrs.	min.	secs.				
I	3	50			29	98	
			10		9	50	3.50.10 L at 8
			20		14	56	
			30		—	78	
			40		23	80	
	3	51	20		22	80	

Shortly after taking this tracing the cat went too deeply under the influence of ether and could be kept alive only by the use of artificial respiration; blood-pressure during the rest of the experiment was very low (50—60 mm. of mercury). It was then found that in the three subsequent tracings the strength of stimulus used above stopped the heart. This is a striking instance of the influence of the condition of the heart upon its sensitiveness to inhibition; the difference in vitality is very marked, and stimulation of the vagus shows a most marked increase in efficiency as the heart beats less vigorously.

Experiment 44 is even more striking; this cat gave three approximately normal tracings; after the third the irritability of the vasomotor and respiratory centres was more or less impaired. Artificial respiration. Tracings 5 and 6 taken from this period show that the rate and blood-pressure had been lowered, and the slowing is much more pronounced with the same stimulus. After taking the seventh tracing too much ether was given, and there was a still further fall of pulse rate and pressure, both of which were now at a very low level (98 beats per minute and 57 mm. Hg. respectively); stimulation with

the weaker of the two currents previously used now caused complete stand-still, which lasted for 52 secs., and it was not until the expiration of six minutes that the heart was able to give even three beats in ten seconds.

Besides such cases of sudden collapse there are others where during a long experiment the heart-beats steadily decline in rate and force. No matter how gradual this decline may be, I have not seen a single case where the efficiency of inhibition did not correspondingly increase. A striking example of it is found in experiment 29, which is given; at least six others show the same thing.

No.	Time			Fractions in secs.	Rate	Pressure	Remarks
	hrs.	min.	secs.				
II	3	55	20		38	180	
			30		13	108	3.55.30 B at 6½
			40		12	114	
			50		21	135	
	3	57			25	156	
			10				3.57.10 Off
III	4	3	10		35	178	
			20		15	120	4.3.20 B at 6
			30		14	120	
			40		22	155	
	4	8	20		24	162	
			30		25	166	4.8.30 Off
			40		31	176	
IV	4	11	40		32	168	
			50		13	104	4.11.50 B at 7
	4	12			12	106	
			10		18	120	
			20		20	128	
	4	18			17	102	
			10				4.18.10 Off
V	4	25	30		32	163	
			40		10	87	4.25.40 B at 6
			50		10	90	
	4	26			18	96	
			10		22	138	
			20				4.26.20 Off
VII	4	54			22	132	
			10		5	58	4.54.10 B at 6
			20		6	53	
			30		10	66	
			40		11	70	
			50		12	72	
	4	56	40		13	92	
			50				4.56.50 Off

As already said, it occasionally happens that the beat of the heart improves as an experiment progresses; the shock of the operation or some other cause may for a time exercise an injurious influence which gradually wears off, so that the heart comes to beat more rapidly and blood-pressure rises. In some of these cases the experimental procedure was such that the efficiency of inhibition could be compared in different tracings, and this was found to diminish as the condition of the heart improved. Two such experiments are 30 and 48, both on dogs.

In the former the rate increased from 20 to 25 or 26 beats per ten seconds. The rise of blood-pressure was even more marked. At first the heart could be brought to rest with the secondary coil at 13 cm. After the improvement in its rate and force of beat stand-still could not be produced with the secondary coil more than $7\frac{1}{4}$ cm. from the primary.

Experiment 48 was upon a young dog, and is noteworthy since (in consequence of the age of the animal?) it was almost impossible to stop the heart. Tracings 6 and 10 were each taken with the secondary coil at 6 cm. from the primary.

No.	Time			Fractions in secs.	Rate	Pressure	Remarks
	hrs.	min.	secs.				
VI	3	34	10		27	115	
			20	$1\frac{1}{2}$	1		3.34.20 R at 6
				$8\frac{1}{2}$	0		
			30	4	0		
				6	2		
			40		3		
			50		5		
	3	37	40		13		
			50		20		3.37.50 Off
X	5	0	20		38	130	
			30		18		5.0.30 R at 6
			40		19		
	5	2	50		24	135	
	5	3		4	10		
				6	18		5.3.5 Off
			10		35	130	

Of course it may be objected to these results that what has been attributed to diminished efficiency of inhibition is only the result of the loss of a certain amount of irritability in the nerve consequent upon exposure or other insult; without denying that this factor plays some part, it must be remembered that the necessity of increasing the stimulus to produce the same effect occurred in every experiment of

the kind whose tracings can be compared; and, I may add, never was it found necessary to do this in the many cases where the opposite change of condition occurred.

We may also measure the efficiency of inhibition by the duration of the initial slowing or stand-still; other things being equal we should certainly consider that inhibition the more effective which is able to maintain itself the longer time.

We have seen that in the vigorous heart of a cat escape is almost immediate, no matter what strength of current be used, and, as a general thing, by the end of twenty seconds after stimulation the heart is beating very much more rapidly than it did during the first three seconds. This curve of escape for the cat is very constant and characteristic. Reference to the tracings of the hearts of weak cats that have already been given will show that for twenty seconds or more there is little or no escape; this delay in the appearance of escape is as characteristic in these hearts with less rapid beat and lower pressure as is the early appearance of the same in strong hearts.

In the dog, on the other hand, it is almost always possible to bring the heart to rest for twenty seconds or more, although the strength of current required to do this varies in different individuals; so that we may consider the duration of stand-still as affording a measure of the efficiency of inhibition. In doing so, however, the same caution applies which has already been given in the discussion of a similar case; we should choose for comparison only hearts which are in decidedly different conditions, so that we may be the more assured that the differences in the duration of stand-still are to be traced back, partially at least, to the condition of the heart, and are not the result of other factors.

It is indeed found that if only those cases are considered which differ but slightly from one another the relation in question does not appear at all; but if we compare tracings which show decided differences the following is found to be true: long stand-stills are the rule in weak hearts, comparatively rare in strong, and especially so in young ones; moreover instances of slight efficiency of vagus stimulation occur only in vigorous hearts.

Beginning with the last statement I find that only in experiments 3, 9, and 48 was vagus stimulation unable to cause stand-still in the dog. In all these cases while there was not a remarkably high blood-pressure nor rapid pulse there was throughout the whole experiment a thoroughly normal pressure and rhythm; nor is the presence of a

supra-normal rate and pressure a fair test of an exceptionally vigorous heart, especially when they are considerably above the normal; a rapid rate may result from accelerator influence and a high pressure from over-constriction of the systemic arterioles, either of which throws extra work upon the heart and so must more or less weaken it; the maintenance throughout a long experiment of a steady rate of 22—25 beats per ten seconds and of a blood-pressure of 116—130 mm. of mercury is, it seems to me, a good sign of a vigorous heart; and this was present noticeably in experiments 3 and 9; in experiment 48 the rate was somewhat higher, 26—28 beats per ten seconds—probably connected with the fact that it was a young animal.

It is thus seen that every case where stand-still could not be produced gave indications of a healthy, vigorous heart; this is not the same thing as saying that vigorous hearts are always hard to inhibit, for some long stand-stills occur with such hearts; unquestionably there are other factors than the nutritional condition of the organ at work to which we must look for the complete explanation of the results; the important point is that the failure to inhibit occurs only in vigorous hearts, while weak ones can always be brought to a comparatively long rest.

Before leaving this part of the subject I should, perhaps, mention an interesting fact which becomes more or less intelligible if weaker hearts give longer stand-stills; in dogs the initial stand-still is almost always of much shorter duration than any subsequent one; it is as if the stoppage of the heart with the concomitant respiratory and other changes exercises an injurious action upon the organ, so that, so, to speak, it is unable to escape so easily from inhibitory influences.

Little need be said of the relation of the condition of the heart to the curve of escape, since such curves are not easily compared with one another; there is, however, one point which should be mentioned; when during the course of two hours the vagus nerve has been stimulated six or eight times, for ten minutes more or less each time, it frequently happens that the heart seems unable to escape successfully from inhibition; at first there is what promises to become the regular curve of escape; *i.e.* the heart is gradually gaining in frequency and force of beat; or, having ceased to do this, is pulsating with a regular and even rhythm; suddenly the beats become more infrequent, finally perhaps ceasing altogether for ten or more seconds; after this escape occurs again, and this escape may be followed by another period of total inhibition; in such cases blood-pressure rises only slightly during

escape, and the impression is made, when one examines such curves, that the mechanism of the heart-beat cannot maintain itself against the inhibitory impulses. These curves will be described more in detail in another part of this paper; whatever may be their true explanation they indicate great efficiency of the inhibitory impulses, and occur only toward the end of a long experiment, when the heart is presumably weaker than it was at first, or else with the use of very strong stimuli. The conditions of their appearance afford very strong evidence that a weak heart is more easily inhibited than a strong one.

To recapitulate the arguments adduced in the above discussion:— 1. In the vigorous heart of the cat no strength of stimulation can cause great slowing, while in a heart which has been appreciably weakened the slowing produced is always decided, and frequently amounts to stand-still. 2. When the heart of the same animal becomes gradually or suddenly weaker in the course of an experiment a decided increase in inhibitory efficiency is noticed; conversely, when the heart becomes stronger during the same experiment, strengths of stimulation which at first were able to cause stand-still are no longer able to do so. 3. Other things being equal, the duration of stand-still or of a certain amount of inhibition is greater in weak hearts than in strong ones. 4. The heart of a dog or a cat, weakened by repeated inhibitions, very frequently toward the end of the experiment shows itself unable to escape effectively to a regular rate and force of beat.

3. Technique of Experiments. Description of the typical Curves of Escape for the Terrapin, the Dog, the Rabbit, and the Cat.

It may be well before going farther to attempt a general description of the curves of escape, or, what amounts to the same thing, the effects of prolonged stimulation of the vagus upon the blood-pressure curve, as studied in different animals.

My experiments were made upon four animals; the terrapin, the dog, the rabbit, and the cat; and one object of this section of my paper is to emphasize the differences in the conduct of these animals under prolonged stimulation. Meyer[1] showed that in cold-blooded animals, in general, vagus inhibition is more effective than it is in warm-blooded animals. In snakes he was able to hold the heart at stand-still for half-an-hour or more; and in one experiment on *Clemmys decussata*

[1] A. B. Meyer. *Das Hemmungsnervensystem des Herzens.* Berlin, 1869.

(Bell), a large turtle from the Antilles, he was able by stimulation of both vagi together to bring about uninterrupted stand-still for an hour; on ceasing the stimulation the heart again began to pulsate. In other experiments on terrapins and turtles he notes spontaneous beats as occurring after a stand-still of ten or more minutes.

I have made experiments upon *Pseudemys mgosa*, and one experiment on a species of *Chrysemys*. From Meyer's account one is led to think that these long stoppages unbroken by any spontaneous beats are the exception among the Chelonia. In every one that I worked with, however, there were absolutely no spontaneous beats for an hour or more; and I am inclined to believe that where proper precautions are taken to keep the nerve irritable and conductive there is no escape whatever from inhibition. In one case I observed a heart for an hour and a half, during which time there was not the slightest sign of a spontaneous beat. From the fact that I have not failed in a single case to prevent escape in these animals, I am inclined to think that, if the experiment be properly conducted, it does not occur; at any rate it must be excessively late in making its appearance[1].

Certainly it is among warm-blooded animals that the phenomenon is best developed, and it is especially as it occurs in the dog and cat that it will be studied in this paper. As the technique of experiment was about the same in all cases, this may be described here. The animal was tracheotomized in order the more easily to regulate the anæsthesia. The anæsthetic varied. Dogs usually received a subcutaneous injection of 1/10 gr. morphia over an hour before the experiment; this was followed by a little ether during the operation. Control experiments were made with ether alone; in some the morphia alone seemed sufficient and no ether was used, the results being, so far as I could discover, the same whether one or another of these anæsthetics was employed.

With cats, ether alone was generally employed; the only objection to its use lies in the difficulty of controlling the amount given; other drugs, especially chloral and paraldehyde, which were tried as substitutes, proved unsatisfactory.

The use of curari was avoided, partly because of the danger of affecting the inhibitory apparatus by an overdose, and partly because it

[1] The above was written before I was aware of T. Wesley Mills's work on the same subject (see this *Journal*, VI. 255. 1885). Reference to his paper will show that my work is a repetition and confirmation of his. It is interesting to note that by stimulation of one vagus he held the heart of a terrapin in diastole for four hours and a half.

is impossible to control the anæsthesia after the drug has taken effect. It is important to know the condition of the animal in this respect, for it is clear that the danger of producing a hyperexcitable central nervous system, especially a hyperexcitable vaso-motor centre, should be avoided as far as possible; otherwise the blood-pressure tracing cannot be relied upon to give us accurate information of events taking place in the heart itself; and this can be avoided only by the proper use of anæsthetics. I have always found that during partial consciousness escape, especially of blood-pressure, is very rapid. The long periods of very low blood-pressure in the medulla resulting from the slowing or total arrest of the heart-beat we know cause dyspnœa, with its concomitant vaso-motor changes; and it is necessary to eliminate this factor as far as possible not only by guarding against hyperexcitability in the medulla but even by lowering its irritability below the normal.

The blood-pressure tracing, taken in the usual way by means of a mercury manometer and a Ludwig's kymograph, was relied upon for the graphic record. It should perhaps be mentioned that a 27% solution of magnesium sulphate was used in the pressure bottle.

Usually both vagi were cut; sometimes only one; the former method is preferable for the study of escape since the curve is not influenced by inhibitory impulses passing down the other nerve; this is of importance, for instance, when one wishes to compare the curves of escape when different strengths of stimulation are used. The nerve was stimulated from a Du Bois Reymond coil, which usually had a large bichromate cell in the primary circuit. In the first fifty-four experiments shielded electrodes were used; the nerve therefore lay on two platinum wires; the results obtained, however, were unsatisfactory and gave much trouble from the impossibility of obtaining uniform contact of the nerve with the platinum; the presence of a greater or less amount of normal salt around the nerve would sometimes escape detection and short-circuit a part or in some cases practically all the current from the nerve. Moreover, as suggested by Gotch and Horsley[1], a nerve should always be stimulated by placing the electrodes on opposite sides, so that the current must go transversely through it. In accordance with this suggestion I had made for this purpose a special pair of electrodes. They consist essentially of a vulcanite bed, one end of which can be made fast in the clamp of a universal holder, and so the whole electrode may be placed in any

[1] "The Mammalian Nervous System," *Phil. Trans. of Royal Soc. of London*, Vol. 182 B. 1891, p. 301.

desired position; a second piece of vulcanite works by a hinge joint upon the first, a light spring holding it down, so that the nerve, which lies between them, is in good contact with both beds but is not injured by crushing; a platinum wire is placed on one side of the upper surface of the lower bed, and a second on the opposite side of the under surface of the upper bed; these wires are the electrodes and the nerve is between them; any current must go through the nerve from one side to the other and so affect every fibre of it equally. The distance between the two electrodes is about six millimetres. It is much easier to keep these hinged electrodes free from too much moisture than the ordinary shielded ones, and one is able to judge fairly accurately from the position of the secondary coil the comparative strength of stimulation, knowing that the contact of the nerve with the platinum is about the same in all cases.

The nerve was kept moist with normal salt solution, in which it lay except during stimulation. Usually the animal was placed in a warm chamber after the completion of the operation; the temperature of this varied from 20° to 25° C.

The chief points which required attention during the experiment were the anæsthesia, which was kept as far as possible just at the point of disappearance of the lid reflex, and the proper contact of the nerve with the electrode, including the prevention of any change of position on the same.

With these remarks on general technique the curves of escape as seen in dogs, rabbits, and cats may be now described. It has already been said that it is very difficult to cause stand-still in the heart of a healthy cat, and associated with this is the rapid and extensive escape from the initial degree of inhibition. In the dog and rabbit, on the other hand, strengths of current which are at first able to produce stand-still permit of only a partial recovery of blood-pressure and of a still less complete recovery of rate; A. B. Meyer records the case of a dog where pulse was kept for one hour at the very low rate of sixty beats per minute by continued stimulation of both vagi; such a thing is not exceptional in narcotized dogs; on the contrary it is the rule. The heart of a cat whose vagi are subjected to the same strength of stimulation would certainly escape in that time to a much higher rate. The difference between the two animals, however, is one of degree and not of kind; the curves of escape in the two cases are essentially the same, that of the cat passing through its phases more rapidly than that of the dog.

When the vagus of the dog is stimulated with a sufficiently strong current to produce stand-still, escape takes place sooner or later. This is usually described as being ushered in by beats of regularly increasing frequency; and at times this does occur, especially with impulses which are just strong enough to stop the heart; it is not, however, an accurate account of what usually happens. The more usual curve is where there are at first a few beats, quite far apart, and the interval of time separating them may be diminished with each new pulsation or not; sometimes the tracing is quite irregular in this respect. Take, for instance, the following:

Exp. 57. Tracing 8. 11.17.20—11.17.30 a.m. The heart gave twenty-nine beats and the blood-pressure was 144 mm. of mercury; both vagi cut.

11.17.30 Right vagus stimulated with secondary coil at 11 cm.; heart stops for $87\frac{1}{2}$ sec.; then escapes as follows—the time in seconds is given for each successive heart-beat:

$25\frac{1}{2}$, 7, $16\frac{1}{2}$, 21, $2\frac{1}{2}$, 15, $5\frac{1}{2}$, $12\frac{1}{2}$, 4.

It may be said that this irregularity is caused by the very long initial stand-still and the profound nutritional changes introduced into the heart thereby. I do not know but that this is true; in point of fact, the above figures are from the last tracing of a rather long experiment; at the same time similar results are obtained when there are not such long initial stand-stills and from the earlier tracings of an experiment; thus in experiment 56, tracing 2, with both vagi cut, a pulse of 28 beats in ten seconds, and a blood-pressure of 135 mm. of mercury, the right nerve was stimulated with the secondary coil at 12 cm.; during the first $4\frac{1}{2}$ seconds of the fall of the blood-pressure curve the heart gave two beats; then followed: none for 21 seconds, then at intervals of $10\frac{1}{2}''$ one; $11\frac{1}{2}''$ one; $14\frac{1}{2}''$ one; $10''$ one beat.

Whatever be its explanation, this result is seen in perhaps half the cases of escape from complete stand-still.

Examples of more regular escape are:—

Exp. 10. Tracing 1. Both vagi cut; left stimulated with secondary coil at 7 cm.; a stand-still of 40 seconds, then beats at intervals of 18, 13 and 4 seconds.

Exp. 21. Tracing 5. Both vagi cut. Left stimulated. Then beats in 24, 11, 7, 6, 6, 3 seconds.

These regular or irregular, but always infrequent beats may be conveniently spoken of as constituting the first period of escape. In

most cases the character of the curve *suddenly* changes to that of the second period in which the heart beats regularly and much more rapidly.

Escape then may be said to be ushered in in one of three ways; (1) by the usual curve, showing the sudden change from the first to the second; (2) by the curve in which there is no sharp distinction between the two periods; (3) where the first period is lacking altogether, the heart passing directly from stand-still into the second period.

Whatever be the way in which escape begins, in the vast majority of cases the blood-pressure tracing is sooner or later a regular curve, the rate of beat and blood-pressure gradually increasing to a certain point, after which it remains approximately constant.

In weakened hearts, on the other hand, after a certain number of such regular pulsations a beat seems to be dropped; there then follows a certain number of regular beats; after which another beat is dropped; and this may continue for a longer or shorter time; usually it gives place to the regular curve; sometimes it continues throughout the whole period of stimulation.

Some time before the end of a long stand-still the low blood-pressure has influenced the vaso-motor centre, causing it to send out powerful constrictor impulses; this is seen in the slight rise which usually occurs on the tracing of stand-still; the vascular system is normally overfilled with blood and the great constriction of the arterioles by diminishing the capacity of the whole system is able to make itself felt in the manometer. This probably explains why, when the regular and comparatively frequent beats of the second period of escape begin, blood-pressure is a little higher for from ten to thirty seconds than it is for a minute more or less afterward. At the same time the pulse also is quicker than it is subsequently, although this increase in rate is by no means so constant as the increase in pressure; sometimes both are absent; it would seem that both are the result of dyspnœa or other secondary influences upon the heart on the one hand and upon the arterioles on the other.

After the first ten or twenty seconds of the second period of escape blood-pressure generally falls slightly, and this is sometimes accompanied by a fall in the rate, which lasts for a variable length of time; then follows a very gradual increase both of pressure and of rate; the latter does not, however, as a usual thing increase very greatly; soon its maximum is reached, and beyond this, though stimulation be continued for thirty minutes or even an hour, there is very little further escape; not so however with regard to pressure; this usually is

found to be increasing noticeably long after the rate has become practically constant; but in long observations it also sooner or later reaches a maximum, which it subsequently maintains.

No absolute figures can be given for the time consumed in these periods of escape; the widest possible variations are met with in different animals, although it seems to be more or less constant for the same animal; I have in vain attempted to find whether the strength of stimulation affects it; but this factor seems to play a very unimportant part.

The extent of escape depends partly upon the strength of stimulation; the stronger stimulus allowing of less complete escape than the weaker (see section 6 of this paper); but it depends chiefly, so far as the factors coming into play in my experiments are concerned, upon the condition of the heart as influenced by the anæsthesia; the more deeply the animal is under the influence of ether or morphia, the lower is the level of pulse and pressure reached; this is especially true of pressure.

How incomplete anæsthesia may affect the blood-pressure tracing through the agency of the central nervous system has already been mentioned; and in this way it affects more or less the extent of escape; the effect moreover is increased by its direct action upon the irritability of the cardiac musculature; we should expect to find, whether the central nervous system interferes or not, that the deeper the anæsthesia the less complete the escape, since the heart is unable then, other things being equal, to beat so forcibly and rapidly.

We have seen that in the anæsthetized dog escape both of rate and of blood-pressure goes to a certain point and little if any beyond that point, no matter how long the stimulation be continued. The question arises whether there is ever complete escape to the original rate and force of beat?

In the narcotized animal there certainly is not in escape from stand-still or from decided slowing; I have not seen a single case of it in the dog, and it is only in the rarest instances that there is even a near approach to it; usually where the pulse is 20—30 in ten seconds and the blood-pressure 130—140 mm. of mercury before stimulation, escape from stand-still rarely goes beyond 12 beats in ten seconds and a blood-pressure of 100 mm. of mercury. 7, 8, and 9 are the more usual figures for rate, and 70 to 90 mm. of mercury for blood-pressure. Extreme care must be taken to avoid poor contact of the nerve with the electrodes; the breathing movements of the animal frequently move the nerve so slightly that the change is unnoticed although the strength of stimulation is sufficiently lessened to permit of more or less complete escape. I may add that no such cases occurred while using the hinged electrodes.

In animals not so deeply narcotized, though by no means conscious, the escape is somewhat more complete: indeed in these cases the pressure sometimes quite reaches the normal.

Upon ceasing the stimulation there is an almost immediate increase in rate and pressure, thus showing that the escape has not been complete; or rather that the inhibitory impulses during stimulation were still effective[1].

The most important fact is that after stand-still the heart escapes to a practically constant level of rate and pressure, and will continue at this level for a long time. It would seem that there are two separate agents at work; the inhibitory impulses on the one hand and the physiological processes which result in the production of the heart-beat on the other; that at first the former get the upper hand; but the latter gradually increase in activity, so that they are able to oppose more and more resistance to inhibition, until at last a point is reached where the two are in equilibrium; that this condition can continue indefinitely; and that, when the inhibitory impulses cease, the other factor, now unopposed, is in many cases able to cause a supra-normal rate and force of beat which lasts for a variable length of time, but which sooner or later gives place to the normal or even to a sub-normal pulse.

The following are the protocols of two typical experiments; in the first the sudden change from the first to the second stage is shown, and this is the usual form; in the second the one stage passes gradually into the other:

EXPERIMENT 60. Tracing VI.

hrs.	Time min.	secs.	Fractions in secs.	Rate	Pressure	Remarks
5	4	20		29	120	
		30		0		5.4.30 R at 9
		40		0		
		50		0		$58\frac{1}{2}$ sec. No beats
5	5			0		
		10		0		
		20	$8\frac{1}{2}$	0		
			$1\frac{1}{2}$	1		$11\frac{1}{2}$ sec. One beat
		30		0		
		40	7	1		7 sec. One beat
			3	2		
		50		9		
5	6			8	63	
		10		7 −		
		20		6 +		

[1] There may be an exception to this statement; it will be described in section 4.

Time hrs.	Time min.	Time secs.	Fractions in secs.	Rate	Pressure	Remarks
5	6	30		7 −		
		40		7		
		50		7		
5	7			8 −	67	
		10		8		
			No tracing until			
5	9			8	80	
		10		8		
			No tracing until			
5	12			7 +	85	
		10		8 −		
			No tracing until			
5	13	40		7 +		
		50		7	81	
						5.14 Off

EXPERIMENT 57. Tracing II.

11	15	20		29	143	
		30		0		11.15.30 R at 11
		40		0		
		50		0		$57\frac{1}{2}$ sec. No beats
11	16			0		
		10		0		
		20	$7\frac{1}{2}$	0		
			$2\frac{1}{2}$	1		
		30	$8\frac{1}{2}$	0		11 sec. One beat
			$1\frac{1}{2}$	1		
		40	6	0		$7\frac{1}{2}$ sec. One beat
			4	1		
		50	$5\frac{1}{2}$	0		$9\frac{1}{2}$ sec. One beat
			$4\frac{1}{2}$	1		$4\frac{1}{2}$ sec. One beat
11	17			3		
		10		5		
		20		6		
		30		5 +		
		40				
		50				
11	18			7	71	
		10		8 −		
		50		9 −		
11	19			9 −		
11	20	40		9		
		50		9		
11	22	10		9 −		
		20		9 −		
11	23	40		9	103	
		50				11.23.50 Off

At times, however, the curve departs somewhat from this form, and the most important of these variations may now be mentioned. The rhythm is not always regular after the beginning of the second period of escape; one form of this has already been described; it consists in the dropping of a beat every now and then; otherwise the pulsations go on as usual. The dropping of these beats is not synchronous with the respiratory movements.

A second kind of irregularity in the curve of escape, or perhaps only an exaggerated form of that just mentioned, makes its appearance frequently after the heart has been subjected to several periods of prolonged inhibition and escape; it is also frequently seen when very strong stimulating currents are used; it consists in alternating periods of pulsation and stand-still; indeed these tracings are strikingly similar to those which Luciani found in isolated frogs' hearts fed for a long time on centrifugalized serum[1]; this may continue for ten or more minutes, indeed through the whole period of stimulation; at other times it gives place to the regular curve of escape, unbroken by periods of stand-still. Sometimes instead of periods of complete stand-still there are simply periods of very great slowing; this form is more commonly met with in the cat.

It sometimes happens, though very rarely in the dog, that, instead of maintaining the level of rate and pressure to which escape has taken place, blood-pressure falls from this level—which may have been kept for several minutes—as does also the pulse.

Stand-still is produced in the rabbit as easily as in the dog, although it does not last so long; the heart rarely remains at rest for thirty seconds. Spontaneous beats then occur, which are at first rather irregular as to rate; eventually a regular rhythm is established, though far below the normal. Gamgee and Priestley record quite rapid and complete escapes in this animal.

My rabbits were under the influence of chloral, and not chloroform or ether as were theirs; at the same time I do not think that this can explain the differences in the results. The following is an example of the results I have obtained and shows how comparatively slight were the escapes.

[1] *Hermann's Handb. d. Phys.* IV, 1, 363

Exp. 38. Large male rabbit. 1 gr. chloral per anum. Both vagi cut. Tracing II.

Time			Fractions	Rate	Pressure	Remarks
hrs.	min.	secs.	in secs.			
3	26	40		32	116	
		50		2	40	3.26.50 R at 7
3	27		7	2	29	
			3	0	26	
		10		0	18	
		20		0	18	
		30		3	36	
		40		4	40	
		50		3	32	
3	28			3	28	
		10		5	28	
		20		5	28	
		30		6	30	
		40		6	30	
3	30	50		9	38	
3	31			9	40	
		10		9	40	
		20		9	38	
		30		9	38	
3	32	50		9	42	
3	33			9	42	
		10		9	42	
		20		26	70	3.33.20 Off
		30		30	95	

I am inclined to look to the character of the electrodes used as explaining the difference; just how these act I do not know; I only know that in using the ordinary catheter electrodes such complete escapes occur in dogs quite frequently; they are rare when shielded electrodes are used; and *never* occur with hinged electrodes; undoubtedly these last insure not only perfect but constant contact with the nerve such as cannot be obtained by the use of either of the other patterns. In view of these facts I must regard such complete escapes as due to errors of experiment.

In all my tracings from this animal (eighteen in all) a certain level of rate and pressure was established; the above protocol is a fair specimen of what always occurred. The number of animals used was not, however, great enough to warrant more detailed statements.

Incidental reference has frequently been made in various parts of this paper to the great resistance of the cat's heart to inhibition; this is shown by the fact that stand-still as a general thing is not obtained;

by the almost immediate commencement of escape; by the greater height to which the pulse and pressure rise while stimulation is being continued, and by the rapidity of this rise. These statements seem to hold for vigorous animals; while among those which give signs of diminished vigour, such as low blood-pressure, or failure to stand the operation properly, tracings are obtained at times which closely resemble those of the dog; it should, however, be added that even under these conditions escape is eventually more complete than it is with the dog.

In the cat also as in the dog we generally find that when the heart begins to escape there is a temporary rise of pressure and sometimes of rate which soon gives place to a fall; afterwards a second rise begins, which eventually reaches a level and remains there for a longer or shorter time. Thus far the curve is almost exactly like that seen in the dog when the stimulation at first only slows the heart to a considerable extent; it differs from such a curve in that its phases are passed through more rapidly; if, however, stimulation be continued for five minutes or more, it is almost always found that a second fall of blood-pressure takes place; as already remarked, this is occasionally seen in dogs; it is the rule with cats. What takes place after this fall varies in different tracings; sometimes the rate and pressure gradually fall until a new level is reached, and this level is practically maintained during the remainder of the stimulation; at other times the fall is succeeded by a rise; then follows another fall, and so alternating periods of rise and fall may continue for an indefinite time; such tracings of escape are frequently seen in weak hearts, and sometimes in strong ones if the stimulating current be of considerable strength. A notable example of it is furnished by Exp. 44, tracing 8; the heart was weakened by repeated previous inhibitions and other insult, and there was general collapse of the animal; blood-pressure was low and all breathing movements had ceased; the animal was kept alive, of course, by artificial respiration. For twenty-four minutes the vagus was constantly stimulated, during which time there were some sixteen periods of alternating greater and less effective inhibition, whether measured by blood-pressure or by the pulse.

The protocol of experiment 29, tracing III. may be given as an example of escape in the vigorous cat. Examples of escape in weak cats have already been given in section 2.

Exp. 29. The heart-beats and blood-pressure are given in successive 10 seconds.

Heart-beat	35	35	15	14	22	27	27	28	28	28	26
Blood-press.	178	178	120*	120	155	170	178	176	176	176	176
Heart-beat	26	24	23	23	26	25	24	24	24	25	23
Blood-press.	176	169	168	171	174	174	170	169	170	171	162
Heart-beat	24	23	23	24	24	25	24	22	25	23	24
Blood-press.	164	164	164	164	170	170	168	162	166	163	162
Heart-beat	25	31	33								
Blood-press.	166	176†	176								

* B at 6. On. † Off.

It will be seen that the heart escaped to 27 or 28 beats in ten seconds and held this for about one minute, a rather short time; the rate then fell to 23 or 25 beats, and remained there until the cessation of stimulation.

Finally, in cats with very high blood-pressure (180—200 mm. Hg) escape is exceedingly rapid and in most cases complete, even though stimuli of considerable strength be used; so that it cannot be said of this animal that the rate and pressure never reach the normal; when, however, they do go so far, continued stimulation will usually lower them again, though to no great extent. This exceptional resistance to inhibition is seen only in the first or second tracings of an experiment; but it is so frequently seen there that it cannot be due to errors of experiment. Its cause lies either in the diminished activity of the inhibitory mechanism or in the greater vigour of the heart; we have no reason, however, to think that the inhibitory apparatus is less active at this time than it subsequently is; and in view of the fact that such tracings occur only when the mechanism of the heart-beat has not been interfered with at all, and, judging from the kymographic tracing, is in good physiological condition, the cause almost certainly lies in the second of the above-mentioned possibilities rather than in the first.

4. The Heart escapes, no matter how slight the initial slowing.

The tendency to regard the escape of the heart as the result of some sort of exhaustion of the inhibitory apparatus resulting from its functional activity has caused physiologists to think of it as taking place only when the heart is either brought to stand-still or is very decidedly slowed; and I have in vain looked for any reference to the

fact, which is easily verified, that it occurs no matter what the amount of initial slowing may be; that this escape from very slight slowing is also comparatively rapid; and that in all cases it is more complete than that from stand-still. Indeed in all my work I have seen but one case where the heart did not escape more or less.

The following protocols give examples of such complete escape with minimal stimuli:

Exp. 32. Tracing V. Cat. Paraldehyde. Shielded electrodes. Intervals of 10 seconds.

Heart-beat	19	19	20	19	19	17	17	18	19	19	19
Blood-press.	120	120	122	121	121	121*	116	120	122	122	124
Heart-beat	19	18	19	19							
Blood-press.	123	122†	126	124							

* On. R at 12. † Off.

Exp. 58. Dog. Hinged electrodes.

Heart-beat	24	24	22	22	22+	22+	22+	23–	23	23	23
Blood-press.	140	140	136*	139	139	140	140	140	140		
Heart-beat	23–	23	23								

hrs.	min.	secs.	Heart-beat	Blood-pressure	hrs.	min.	secs.	Heart-beat	Blood-pressure
2	58	30	23	138	3	4	50	23–	128
3	0	20	23		3	5		23–	131†
		30	23	134			10	23–	129
3	2		23–				20	23	129
		10	23	131	3	7		23	
3	3	40	23–				10	23	137
		50	23–	131					

On. R at 14. † Off.

A dozen similar examples might be added, taken from as many experiments both on dogs and cats. In fact whenever the heart was slowed but two or three beats every ten seconds escape took place nearly or quite to the normal, and the rate and pressure thus reached was maintained throughout any length of stimulation.

The time taken for the completion of escape is very short, seldom over one minute; shorter, in other words, than when stronger stimuli are used and great slowing or stand-still at first produced.

5. Rapidity of Recovery by the Inhibitory Mechanism of the Power to produce Stand-still.

The reader is probably familiar with the fact that a very short time is required for the recovery of inhibitory power after the cessation of stimulation; if stimulation be stopped as soon as escape from stand-still begins, the heart can be stopped again after the lapse of ten or twenty seconds; and often it is found that the duration of this second stand-still is quite as long as the first. Take the following example:

Experiment 10. Tracing 5.

	Dog	Shielded Electrodes	
1.	Both nerves stimulated	25 sec.	0 beats
2.	„ „	6 „	1 beat
3.	„ „	9 „	6 beats
4.	Off for 32 sec.		
5.	Both nerves stimulated	24 sec.	0 beats
6.	„ „	8 „	1 beat
7.	„ „	8 „	5 beats
8.	Off for 16 sec.		
9.	Both nerves stimulated	20 sec.	0 beats
10.	„ „	6 „	1 beat
11.	„ „	10 „	7 beats
12.	Off for 14 sec.		
13.	Both nerves stimulated	18 sec.	0 beats
14.	„ „	6 „	1 beat

The duration of the necessary rest is not equally brief in all cases, but it is doubtful whether it ever requires more than 30—40 seconds to insure complete recovery.

If, instead of shutting off the current as soon as the heart begins to beat spontaneously, escape be allowed to take place for fifteen or more minutes it is found that even here a scarcely longer time is needed for the restoration of complete inhibitory efficiency. Thus in experiment 23, stimulation continued from 2 h. 58 m. 30 sec. until 3 h. 35 m. 45 sec. The initial stoppage was 25 seconds, and at the end of stimulation the rate established was 7–8 beats per 10 seconds with a blood-pressure of 105 mm. Hg. The current was off from 3 h. 35 m. 45 sec. until 3 h. 37 m. 20 sec., *i.e.* for 1 m. 35 sec.: on stimulating again with the same strength of current the heart was stopped for 43½ sec., and the curve of escape was about the same after this short rest as it had been during the first stimulation.

This has an obvious bearing on the question whether escape is an

exhaustion phenomenon at all; it is, of course, possible that complete recovery from exhaustion may take place in such a short while, but it is against all analogy: and one is led at least to suspect that other physiological processes are at the bottom of it.

6. Relation between the Strength of Stimulus and the Curve of Escape.

The object of this section is to compare the curves of escape obtained with different strengths of stimulation. It will be convenient to treat the subject under the following heads:

1. Relation of the strength of stimulation to the duration of stand-still.

2. Its relation to the extent of escape, both of rate and of pressure.

3. Its relation to the duration of escape; *i.e.* to the time consumed in reaching a constant level of rate and of pressure.

The difficulty of investigating any of these problems must be at once apparent; it has been shown that the weaker the heart, the more effective is the same strength of inhibitory impulse; and the conditions of most of my experiments preclude the possibility of the heart's being in the same condition during any two tracings. It cannot be but that very prolonged inhibition, say for ten or fifteen minutes, with the slow pulse and low blood-pressure consequent thereupon, profoundly modifies the physiological condition of the organ. The long-continued anæsthesia also must have its effect in weakening the heart; and in point of fact it is found that during an experiment of two hours' duration the heart is almost always weaker at the end than it is at the beginning.

But apart from this uniform fall of cardiac vitality and concomitant rise of inhibitory efficiency there must always be temporary variations in the physiological condition of the organ; changes in the depth of anæsthesia or in the vascular and respiratory mechanisms may at any time affect the force of the beat or the activity of the inhibitory mechanism, and these variations cannot be entirely prevented even with the utmost care and skill. We must therefore think of the curve of inhibitory efficiency as showing, not a gradual rise, but a rise which is broken by temporary falls; indeed we have already seen that at times it represents a fall; and at other times, no doubt, the mean of the two curves is met with; *i.e.* where there are temporary rises and falls, but on the whole no decided change.

The difficulty of the experiment is the more apparent when we

remember that these changes of inhibitory efficiency not only cannot be avoided, but cannot even be discovered except by actually causing inhibition; they depend upon two variable factors, of which the said efficiency constitutes the algebraic sum, so to speak, the condition of the mechanism of the cardiac beat, and the condition of the inhibitory mechanism itself. The only ready means we have of estimating the former is by the blood-pressure curve, and this we know depends both on cardiac and extra-cardiac events; and we have no means whatever of estimating the latter. It is, therefore, to be expected that the experimental investigation of the problem proposed in this section will not always lead to uniform results; the utmost we can hope for is that in a great number of experiments the relation will in some degree become apparent.

1. *Relation of the strength of stimulus to the duration of stand-still.* Evidence on this point may be gathered from almost all of my experiments on dogs, since in most of them the heart was stopped with stimuli of different strengths. The greater number of these experiments were made, however, with other objects in view and thus certain complications were introduced. A number of experiments were therefore made in which stimulation was continued only through the stand-still, and was stopped as soon as the first or second spontaneous beat had occurred; from five to ten minutes elapsed between any two tracings, so that proper time was given for recovery. For the convenience of the reader the results of these experiments are tabulated according to the strengths of current employed:

Exp. 1.	Secondary coil at	5		6		8		10			
	Heart stopped for (secs.)	37, 34		30		34, 33, 33		44* 32			
Exp. 4.	Secondary coil at	3	4	5	6	7	9	11	12	14	
	Heart stopped for (secs.)	26	22	22	21	24, 23	12*	24	23	25	
	Secondary coil at	16	18	19	20						
	Heart stopped for (secs.)	25	22	22	0						
Exp. 40.	Secondary coil at	3	4	7	9	11	12	$12\frac{1}{4}$			
	Heart stopped for (secs.)	57, 67	48	65	49	21*, 57	72, 69	64			
	Secondary coil at	12.6	$12\frac{3}{4}$	13							
	Heart stopped for (secs.)	29	28	17, 13							

Exp. 43.	Secondary coil at	3	4	7	8	9	10	11
	Heart stopped for (secs.)	80	71, 83	82	90, 104	88	81	73, 90
Exp. 58.	Secondary coil at	7		10		$10\frac{1}{2}$		11
	Heart stopped for (secs.)	56, 60		68, 82, $75\frac{1}{2}$, $64\frac{1}{2}$		79		21
Exp. 59.	Secondary coil at	6		8			10	
	Heart stopped for (secs.)	$86\frac{1}{2}$, 81		$83\frac{1}{2}$, $91\frac{1}{2}$, 85, 86			$73\frac{1}{2}$, 100	

A study of these figures shows that with moderately strong currents the duration of stand-still is practically independent of the strength of stimulation: or in general, when the secondary coil is anywhere from 11 to 7 cm. from the primary, the duration of stand-still is about the same for all stimuli; in some experiments this is beautifully shown, notably in 1, 4, 43, and 59. The differences here are so slight that we must regard them as accidental. Further inspection suggests that if the current be just strong enough to stop the heart, stand-still lasts for a much shorter time than with stronger currents; this fact has been noticed in many experiments; of those just quoted 40 and 58 are cases in point; in each of these the secondary coil was moved up carefully and the point accurately found at which stand-still was produced, in the former case at 13 cm., in the latter at 11, and it will be seen that the duration of stand-still produced with these stimuli is very brief compared with that resulting from stronger stimulation[1].

It should be remembered that in these experiments strong and weak currents were alternated in order so far as possible to exclude errors arising from variations in the efficiency of inhibition. One other matter should be mentioned; I have already said that it frequently happens that the initial stand-still is shorter than those which follow. In the above table I have marked these with an asterisk whenever they happen to be given.

Certain of the above experiments (*e.g.* 58) seem to indicate that very strong stimuli do not stop the heart quite so long as weaker ones;

[1] Professor Howell, to whom I am indebted for many useful criticisms upon this paper, has suggested that the failure of minimal stand-still stimuli to cause as long arrest of the heart-beat as that caused by stronger stimuli may be due to the running down of the bichromate batteries used in the primary circuit. This may be true, as no special precautions were taken in these particular experiments to avoid such an error. But the same factor had occurred to me in many other portions of the work, and I frequently used the control of sending the current through the primary coil for three or four minutes before sending the secondary current into the nerve. So far as I could see this did not affect the result.

if this be true, it is easily explained by supposing some injury to the nerve.

We may, therefore, conclude that minimal stand-still stimuli do not stop the heart so long as stronger ones; but that, if the strength of current be slightly increased, a point is soon reached beyond which any increase produces little or no change in the duration of stand-still.

2. *Relation of the strength of current to the extent of escape, both of rate and of pressure.* It has already been shown that escape of the heart takes place no matter what may be the amount of slowing caused at first; the problem for investigation in this section, therefore, is the extent of escape from different amounts of initial inhibition.

Reference to the results already given will show that where the initial slowing amounts to only one or two beats in ten seconds, escape is almost or quite complete. If the inhibition be more decided, escape is not so complete, although it always takes place, and it may be stated as a general rule that the greater the initial slowing the less rapidly will the heart beat when its final level of escape is established. Thus, in experiment 56, tracing I, the following result was obtained.

Exp. 56. Dog. Both vagi cut. Hinged electrodes. Intervals of 10 secs. Tracing I.

Heart-beat	29	16	14	15	17	20	20	20	20	21 +	23	23
Blood-press.	132	107*	104	103	97					132		
Heart-beat	24	24	24	24	24	25	25		26†	27	24	
Blood-press.				144						144	143	

* On. R at 13½. † Off.

The results of the above tracing are plotted in fig. 1, together with the curve of escape from stand-still as shown by the next tracing of the same experiment; it will thus be seen at once that in the latter case escape is much less complete.

Not only should the effects of stimuli be compared one of which slows while the other stops the heart, comparisons should also be made between the effects of two stimuli, each causing stand-still, but one stronger than the other; will the stronger current allow of more or of less complete escape than the weaker? For the present let us confine our attention to the rate. The matter must be investigated by comparing different tracings taken from the same animal, different strengths of stimulation being used in different tracings; it is evidently best, moreover, to select two strengths of current and to use these alternately; we shall thus be able to compare the effects of the same stimulus at

different times, and so discover if there have been any decided change in the sensitiveness of the heart to inhibition.

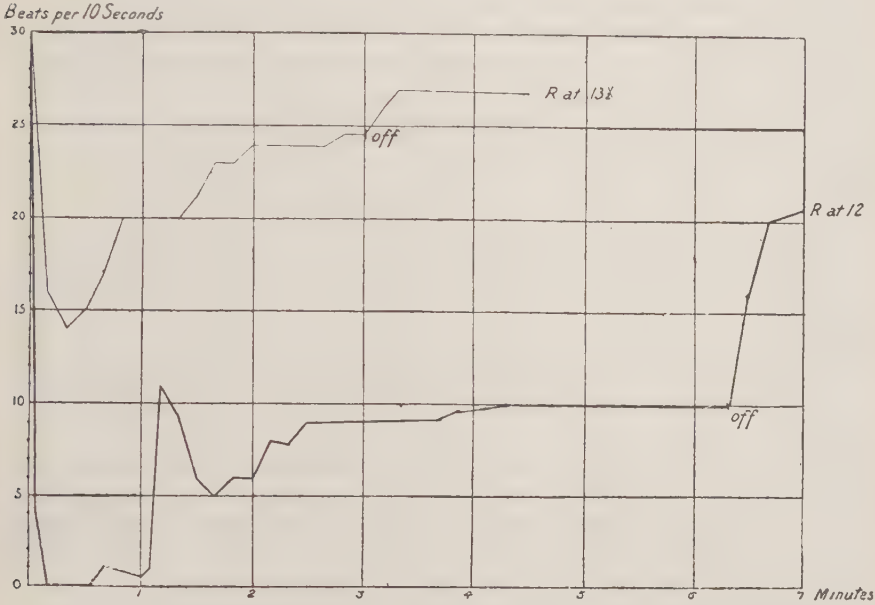

FIG. 1. Exp. 56, I. and II. Curves of escape. Ordinates represent number of heart-beats in 10 seconds. Abscissæ represent time in minutes from the beginning of inhibition.

This, indeed, is the only way in which the question can be investigated; but it presents a complication, which must be constantly taken into account since it cannot be entirely avoided. This complication arises from the long periods of low blood-pressure which such treatment of the heart necessarily produces; one would suppose beforehand, from what has been said of the relation between the condition of the heart and the efficiency of vagus stimulation, that, even were the stimulus the same in all cases, it should be found more effective with each new inhibition. And this is more or less true; in two experiments where the same strength of current was actually employed during all tracings there was less complete escape in the last of the six tracings than in the first. Close inspection of these curves however shows that the increase of efficiency as measured by the extent of escape is not uniform; that in the first tracing, before anything had been done to the heart, escape is much more complete than it is in any subsequent tracing; that for three or four tracings after the first one there is little variation in the effect produced; the heart seems to withstand the insults offered to it

for this length of time; and it is only afterward that the effects of exhaustion make themselves felt. If six tracings be taken, for instance, the sixth and frequently the fifth will show much less complete escape than the second, third, and fourth. In these experiments stimulation continued for ten minutes, more or less, a rest of ten or more minutes was then given before the next tracing was taken.

The results of these two experiments only confirm what appears to a greater or less degree in all my work on the question under discussion in this section of my paper; and I think the conclusion may be safely drawn, that, if in a great number of experiments we compare the second, third, fourth, and sometimes the fifth tracings of escape from stand-still, we may hope for a satisfactory answer to our question; at times the first will be given also, and, if there is no sign of a weakened heart, the sixth and seventh may also be taken.

Thirteen experiments upon this point were made on dogs; most of them were with the ordinary shielded electrodes, and while their results justify the conclusion drawn from those obtained with hinged electrodes I shall give the results of the latter experiments only, since these are perfectly uniform and for obvious reasons much more reliable. The following is a tabulated *résumé* of these results.

EXPERIMENT 55.

Tracing	Stimulation	Initial stand-still in seconds	Escaped to: Rate, in beats per 10 secs.	Escaped to: Pressure, in mm. of Hg
III	R at 9	26	6	104
IV	R at 7	37½	5 +	91
V	R at 10	94½	9 +	128
VI	R at 5	34	6 +	59

EXPERIMENT 56.

II	R at 12	21	10	102
III	R at 9	69	9	99
IV	R at 12	48½	10	115
V	R at 9	87	7	87

EXPERIMENT 57.

II a	R at 11	57½	9	103
b*	R at 10	88	6	76
III	R at 9	105	5 +	70
VI a	R at 11	7	11	83
b	R at 9	43	8	
VII	R at 9	86	6 +	75

* Means that after the heart has established a rate of nine beats per ten seconds, the current was strengthened by moving the secondary coil to 10 cm.

EXPERIMENT 60.

I	R at 9	—	7	82
II a	R at 12	41	14	107
b	R at 9	$38\frac{1}{2}$	8+	81
III	R at 9	62	9	90
IV	R at $11\frac{2}{3}$	slowed	25	115
V a	R at 11	$56\frac{1}{2}$	12	99
b	R at 9	$28\frac{1}{2}$	7+	72

EXPERIMENT 61.

I	R at 9	50	2	30
II a	R at 12	$28\frac{1}{2}$	15	100
b	R at 9	58	—	—
III a	R at 9	62	4	62
b	R at 7	slowed	4	62
IV a	R at 11	61	16	102
b	R at 9	87	4+	48

For the clearer understanding of what follows some of these results have been plotted in figs. 2—4; each figure contains two curves, one showing the curve of escape with the weaker stimulus, the other the curve of escape with the stronger stimulus. The abscissæ represent time in minutes from the beginning of escape, the ordinates the number of heart-beats in ten seconds; the lighter lines give the result of weaker stimulation, the heavier lines that of stronger stimulation.

Beyond showing that the stronger stimulus permits less complete escape, these figures bring out another fact; there is in the escape with stronger currents a tendency to irregularity of rate; a certain pulse is reached but it is not maintained; a minute or more later the heart is found to be beating more slowly; then it beats more rapidly; then more slowly, and so on. This is in marked contrast with what occurs with the weaker stimulus, that which is just able to cause stand-still, for instance; here the heart steadily escapes to its level[1] of rate and maintains this level as long as stimulation continues. An extreme case of this irregularity with strong currents is where periods of total inhibition alternate with a group of beats. It is unnecessary to point out that this is exactly what occurs toward the end of an experiment with almost any strength of current and has been explained by the exhaustion of the heart. It is a significant fact that strong stimuli can produce this effect long before weaker ones are able to do so.

[1] Disregarding the first rise which appears in many cases.

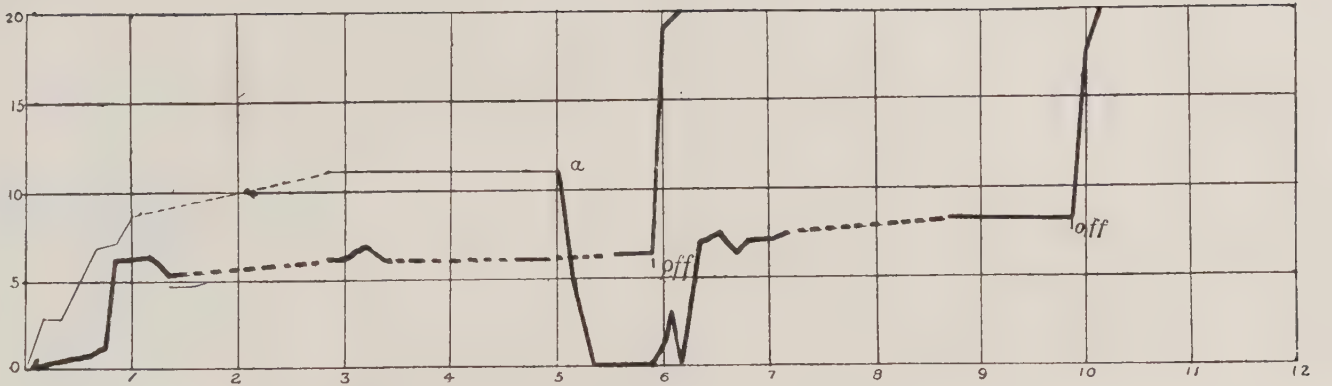

FIG. 2. Exp. 57, VI. (R at 11, followed at *a* by R at 9), and VII. (R at 9).

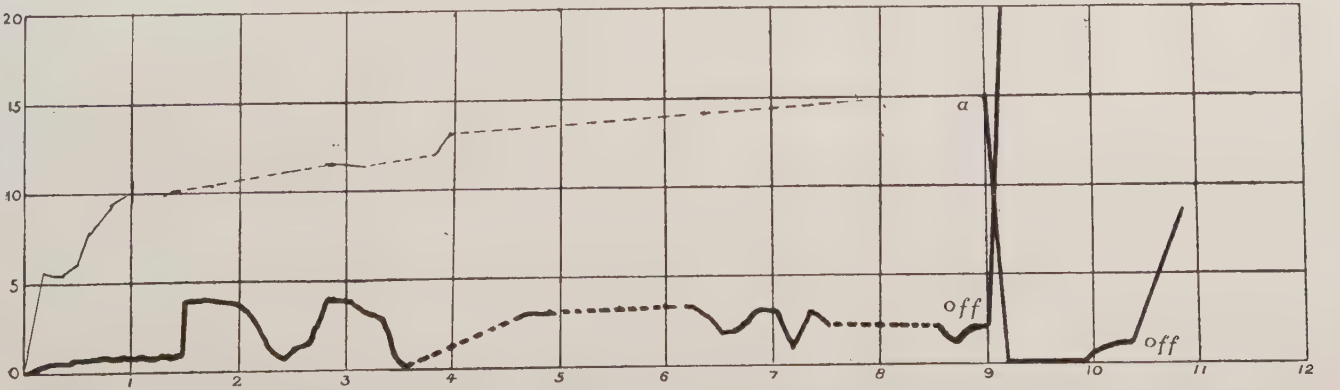

FIG. 3. Exp. 1, I. (R at 9), and II. (R at 12, followed at *a* by R at 9).

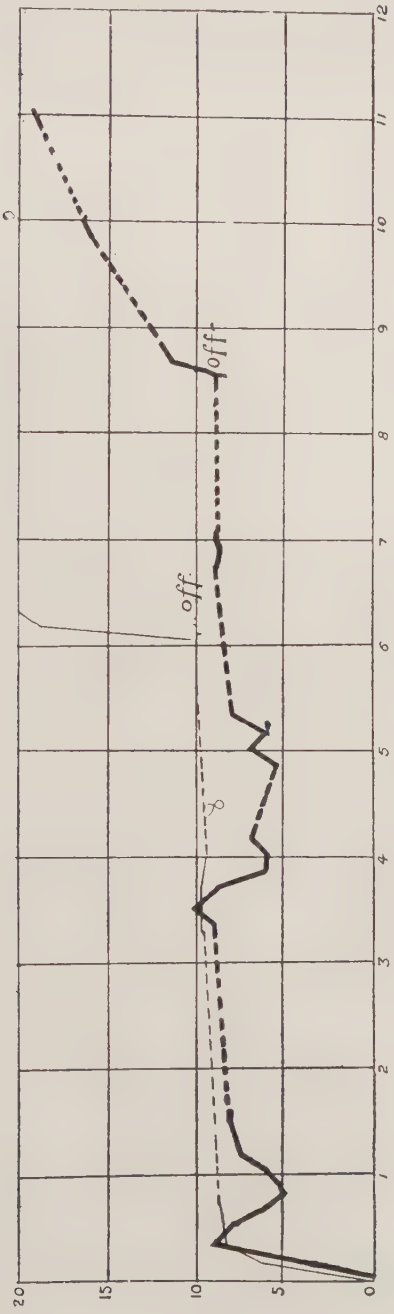

FIG. 4. Exp. 56, III. (R at 9), and IV. (R at 12).

In the above discussion only the rate has been taken into account; and under the conditions of these experiments this, of course, is a better test of the work of the heart than is blood-pressure; reference to the tables given on pages 192–3 will, however, show that the level of blood-pressure established in escape is lower with the stronger stimulus.

If in such an experiment while the weaker stimulus is being used the secondary coil be moved up to the position which gives the stronger stimulus, we obtain the result shown in experiments 57, 60, and 61 of the above tables; the heart is either brought to rest or greatly slowed; escape then takes place, but goes on only as far as the point reached in other tracings when this stronger stimulus is the one first employed; the curve, in other words, is the same as when that strength of stimulation is given to a normal heart and not to one already inhibited. This is not true, however, when very strong currents are used; if, for instance, the first stimulation be with the stronger current (secondary coil at 8—9 cm.) and after the rate of escape is well established the current be further strengthened, it will frequently be found that no effect whatever is produced; this is almost what happened above in experiment 61, tracing 3; here moving the secondary coil to 7 cm. caused a temporary fall, but escape soon took place to the original rate and pressure. An example may be added in which no effect whatever was produced.

Exp. 56. Dog. After escape from stand-still with the secondary coil at 9 cm., we have:

No.	Time			Fractions in secs.	Rate	Pressure	Remarks
	hrs.	min.	sec.				
VII	2	2	50		7	58	R at 9
	2	4	20		7	75	
	2	7	20		7	76	
			30		7	76	2.7.30 R at 6
			40		7	79	
	2	8	20		7	72	
			30		7	74	2.8.30 R at 0

The explanation of this is evidently that the point of maximal stimulation has been reached. This varies greatly with changing conditions; generally in my experiments it was when the secondary coil was at about 8 cm.

This is important in showing that the strength of stimulation may be considerably increased beyond the point which causes stand-still before maximal effects are produced; and that the inability of a stronger stimulus to cause longer stand-still than that caused by the weaker is not to be explained on the assumption that we have passed the point of

maximal stimulation, since, if the stronger stimulus allows less complete escape than the weaker, stronger impulses actually reach the heart. Indeed on the whole I am inclined to think that the stronger stimulus, other things being equal, stops the heart longer than the weaker; but that soon after we pass the minimal stand-still stimulus the differences in the duration of stand-still are so slight that they are obscured by the action of other factors.

3. *Relation of the strength of stimulus to the duration of escape;* or, to speak more accurately, to the length of time elapsing before the heart ceases to increase the rate and force of beat despite the continued stimulation. Little more can be done than to indicate this as a more or less probable way in which a difference in the strength of stimulus may make itself felt; I have made no experiments with this point specially in view, and do not think that the method used of obtaining a graphic record enables one to make accurate determinations of the time relations.

This much, however, is apparent even in my tracings; the escape from minimal slowing never occupies more than two minutes from the beginning of stimulation, while, if the initial inhibition be greater or amount to actual stand-still, more time than this is always consumed.

When we come to compare the time relations of two curves of escape, each from stand-still but from different strengths of stimulation, we find that this is difficult, if not quite impossible; the tendency to irregularity of rhythm frequently makes it difficult to say at what moment escape has ceased; and the differences in time are so slight that they are generally obscured by secondary factors; we can therefore compare only those curves which show a steady increase in rate and force to the escape level of pulse and pressure.—Only this can be said: if the comparison be made between the results of minimal stand-still stimulation and stronger stimulation it will be found that the former reaches the final escape rate of the latter sooner than the latter itself does. Thus in experiment 56 we have:

No. of Tracing	Stimulus	Final escape rate	Time required to reach this rate	Remarks
III	R at 9	9	Over 6 mins.	This rate was reached in II. (R at 12) in less than 2 mins.
V	R at 9	7	Over 5 mins.	This rate was reached in IV. (R at 12) in a little over 1 min.

7. On Alternate Stimulation of the Vagi.

No study of the escape of the heart would be complete without consideration of the results of alternate stimulation of the vagi. The subject has been studied by Tarchanoff and by Gamgee and Priestley with more or less conflicting results. Tarchanoff[1] stated that after the heart of a mammal had begun to escape from inhibition by one nerve shunting the current into the other is unable to again cause stand-still. Gamgee and Priestley[2] repeated this work, and concluded that "continued stimulation of one vagus never annulled or even prejudiced the inhibiting powers of the other unless the inhibiting apparatus had been recently kept under stimulation for some time[3]."

I shall not attempt here to discuss the work of those investigators; my own experiments have not been altogether satisfactory, and I hope at some future time to investigate the subject. This much, however, can be said; both Tarchanoff and Gamgee are right in what after all is the main point; after prolonged stimulation of one nerve shunting the current into the other has no effect whatever[4]; as an example of this take exp. 6, tracing 14.

1. L at 9. Heart stops 25 secs.; then
2. „ „ 4 „ 1 beat
3. „ „ 10 „ 10 beats
4. Nerve slipped off the electrodes and the heart beat normally for 21 sec.; then
5. R at 9. Heart stops 16 secs.; then
6. „ „ 98 „ 98 beats
7. L at 9. „ 22 „ 22 beats
8. R at 9. „ 6 „ 6 beats
9. Stimulation ceases.

Similar results occurred over and over again, so that we may regard it as established that, during prolonged escape from the effects of stimulating one vagus, shunting the current into the other does not change the rate of beat.

Summary of Results.

The experiments given in this paper show that the escape of the heart from vagus inhibition is not the result of the exhaustion of the

[1] *Archives de Physiologie*, Serie II. T. II. 1875.
[2] This *Journal*, I. 39. 1878. [3] *Loc. cit.*, p. 40.
[4] Perhaps it should be added: unless the two vagi have different inhibiting power.

inhibitory fibres of the nerve either by continued stimulation or the conduction of nervous impulses; that the more vigorously the heart is beating when the nerve is stimulated, the less efficient is inhibition, and *vice versa*; that the efficiency of inhibition varies greatly in different animals, there being usually no escape in the terrapin while the heart of a cat can rarely be brought to complete stand-still; that in all animals in which the phenomenon of escape is well marked, the heart escapes to a certain rate of beat and maintains this rate so long as the same strength of stimulation is continued; that this is true not only when the initial inhibition amounts to stand-still, but also when the heart is merely slowed; that the escape rate which is finally established depends upon the strength of stimulation of the vagus nerve, the pulse being quicker and blood-pressure higher with weaker currents than with strong ones; that in escape from stand-still, shunting the current into the other vagus cannot bring the heart to rest unless the inhibitory power of the two nerves be different; and that one or two minutes, at most, after a prolonged (say, ten minutes) period of inhibition the same current will produce practically the same curve of inhibition as before, the stand-still being as long and the escape neither more rapid nor more complete. It is also an interesting fact that after we go beyond the minimal stand-still stimulus, the duration of stand-still seems to be independent of the strength of stimulation although the subsequent curve of escape shows that we are by no means dealing with maximal currents.

Concluding Remarks. The rapidity of recovery by the inhibitory mechanism of the power to produce stand-still, the effects of alternate stimulation of the vagi, the peculiar characters of the curve of escape—especially the establishment of a certain escape level of force and rate of beat—the relations of this curve to strength of stimulus employed, all suggest, at least, that something else than fatigue of the inhibitory apparatus is the cause of escape.

On the other hand, the fact that inhibition is more effective in weak hearts than in strong ones enforces the conception that inhibition is a resistance of some sort to the execution of the events of the heart-beat; a resistance, in other words, to the activity of a powerful automatic mechanism, and this suggests at once the familiar conception of resistance in the physiology of the respiratory centre.

I am strongly inclined to think that we must seek here the explanation of the phenomena of escape, and shall close this paper with a brief statement of the view I am inclined to hold with regard to it.

Inhibition is a resistance to the occurrence of those katabolic changes which yield the energy for the heart-beat. Let us suppose that these changes are carried out in such a way that when resistance is opposed to them they can "gather head" against it and ultimately overleap it. This idea, of course, is not new to the literature of the physiology of the heart-beat[1]. On opposing a slight amount of inhibitory resistance, therefore, we should slow the beat, since between any two contractions time would be consumed in "gathering head" against resistance and so the diastole lengthened. Stand-still would thus be caused by resistance of such amount that considerable time must elapse before the beat can be produced against it; the heart of a cold-blooded animal shows the phenomenon of escape but slightly if at all because the automatic mechanism of the beat is not so powerful and hence is unable to overcome inhibitory resistance. The final "escape level" would be the establishment of equilibrium between the katabolic changes of the beat on the one hand and the resistance on the other; the greater the resistance the slower must be the final rate established. Finally, the *gradual increase* in the rate and force of beat to the escape level is an expression of the "staircase phenomenon"; when the heart has once overcome the resistance and given one contraction, the giving of that contraction makes the next one an easier matter against the same resistance, so that it comes sooner than the first; the third similarly comes sooner than the second, and so on until everything has adjusted itself to the changed conditions produced by the presence of the factor of inhibitory resistance.

[1] Cf. Howell and Cooke, This *Journal*, XIV. 198—220. 1893.

VITA.

The writer of this paper was born in Fort Royal, Warren County, Virginia, June 19, 1865. He received his elementary education in elementary and high schools of Virginia and Maryland, matriculating at the Johns Hopkins University in the summer of 1883. He received from the same University the degree of A.B. in June, 1886, after which he spent three years as an instructor in McDonogh School, Baltimore County, Maryland. Returning to the Johns Hopkins University in the autumn of 1889, he pursued for four years graduate studies in Biology; he was Junior Assistant in Physiology and Histology, 1890-92; and Fellow in Biology, 1892–93. His major subject for the degree of Doctor of Philosophy was Animal Physiology, and his minors were Animal Morphology and Chemistry.